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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,038	04/01/2005	Douglas W. Losordo	57987(71417)	2908

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EXAMINER	
RAE, CHARLESWORTH E	

ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,038	LOSORDO, DOUGLAS W.	
	Examiner	Art Unit	
	Charleswort Rae	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01/08/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *4,5,13-5, 17-32 and 38-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-12,16 and 33-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/1/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the election requirements, filed 1/8/08, and supplemental response, filed 2/7/08, electing the below species, are acknowledged:

1) SKI-606 (as a single disclosed chemically defined inhibitor of vascular endothelial growth factor-mediated vascular permeability);

2) intravenous infusion ("2a" - as a single specific route of administration);

3) Myocardial infarction ("3a" - previously elected as a single specific ischemic type); and

4b) inhibitor of vascular endothelial growth factor-mediated vascular permeability is not administered as part of the cardioplegia solution.

Status of the Claims

Claims 1-41 are currently pending in this application.

Claims 4-5, 13-15, 17-32, and 38-41 are withdrawn for being directed to non-elected subject matter.

Claims 1-3, 6-12, 16, and 33-37 are presented for examination.

Election

Applicant's traversal argument fails to point out any specific error in the election requirement response. Thus, applicant's response is considered to be without traverse.

Claim of Benefit

It is noted that no support is found in provisional application 60/416,334, filed 10/25/02, to support applicant's assertion of claim of benefit with respect to SKI-606. The genus of inhibitor of vascular endothelial growth factor-mediated vascular permeability is disclosed, wherein pyrazolopyrimidin inhibitors, PPI or PP2, are

disclosed as a apparent subgenuses in the provisional application (see claims 1-18). Also, a specific inhibitor compound species is exemplified having the chemical formula C16H19N5 is disclosed (see claim 5). However, SKI-606 is not expressly disclosed nor is any specific guidance or direction disclosed to make and use SKI-606 . For these reasons, applicant is not found to have had possession of the claimed subject matter with respect to SKI-606. For examination purposes, the effective filing date for claims embodying SKI-606 is deemed to be 10/03/03, which is the filing date of the corresponding PCT application (PCT/US03/31430= WO 2004/032709). Applicant is invited to point out to the examiner where support can be found in provisional application for the instant claimed SKI-606 (i.e. the specific page, paragraph, and line number where support may be found).

Claim rejections – 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 6-11, 16, and 33-37 are rejected under 102(e) as being anticipated by Boschielli et al. (US Patent Application Pub. No. 2003/0212276).

Independent claims 1 and 33 recite "[a] method for treating, preventing, or reducing reperfusion injury following ..., by administering an inhibitor of vascular endothelial growth factor-mediated vascular permeability, ..." The term "preventing," given its broadest reasonable possible interpretation is construed to mean absolute absence of any evidence of reperfusion injury or a complete cure of the underlined disease. Thus, the instant claims read on all methods of treatment comprising applicant's active method step of administering the elected compound species (SKI-606) to any subject with or without myocardial infarction are reasonably encompassed by the instant claims.

Boschelli et al. (US Patent Application Pub. No. 2003/0212276) teach compounds that are useful for treating cancer, including 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methyl-1-- piperazinyl)propoxy]quinoline-3-carbonitrile, which has the identical chemical structure to applicant's elected compound species, SKI-606 (abstract and para. 0100; see also para. 0006-0036). Boschielli et al. is silent regarding the term "administering." However, it is the examiner's position that someone of skill in the art would reasonably construe the teaching of Boschielli et al. that 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-methyl-1--piperazinyl)propoxy]quinoline-3-carbonitrile to imply the administering of the exemplified compounds to a person with cancer in order for said compounds to be useful to treat cancer (see abstract). Thus, the term "by administering an inhibitor of vascular endothelial growth factor-mediated vascular permeability" as recited in claims 1 and 33,

given its broadest reasonable possible interpretation, is construed to be impliedly taught by Boschelli et al.

For the above reasons, claims 1-3, 6-11, 16, and 33-37 are found to be anticipated by the cited reference.

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 6-12, 16, and 33-37 are rejected under 103(a) as being unpatentable over Boschelli et al. (US Patent Application Pub. No. 2003/0212276) and Cheresh et al. (US Patent Application Pub. No. 2003/0130209).

The above discussion of Boschelli et al. is incorporated by reference. Boschelli et al. do not teach a method of treating myocardial infarction or the intravenous administration of the exemplified compounds.

Cheresh et al. (US Patent Application Pub. No. 2003/0130209) is added to show the general state of the art regarding the intravenous administration of a pyrazolopyrimidine class Src family tyrosine kinase inhibitor for treating a subject suffering from myocardial infarction. Cheresh et al. teach a method for treating a patient suffering from a myocardial infarction comprising administering to the patient a therapeutically effective amount of a pharmaceutical composition comprising a chemical Src family tyrosine kinase inhibitor, wherein the chemical inhibitor is selected from the group consisting of a pyrazolopyrimidine class Src family tyrosine kinase inhibitor, a macrocyclic dienone class Src family tyrosine kinase inhibitor, a pyrido[2,3-d]pyrimidine class Src family tyrosine kinase inhibitor, and a mixture thereof (see reference claims 1-2). Claim 1 and claim 33, for example, recite "myocardial infarction. Cherish et al. teach compositions comprising said compounds are administered intravenously (para 0060-0061). Instant claim 12 recites the term "intravenously." Cheresh et al. teach that the methods of the present invention are well suited for the specific amelioration of VP induced tissue damage, particularly that resulting from myocardial infarction, because the targeted inhibition of Src family tyrosine kinase action focuses inhibition on VP without a long term effect on other VEGF-induced responses which can be beneficial to recovery from injury (para 0105). Cherish et al. teach that the use of synthetic, relatively small-molecule chemical inhibitors is in general safer and more manageable that the

use of the relatively larger proteins (para 0107). Thus, the former are preferred as therapeutically active agents (para 0107).

Based on the teaching of Cherish et al. that synthetic small molecules are in general safer and more manageable than the use of relatively larger proteins, someone of skill in the art would have been motivated to combine the teachings of the above cited references to create a method for treating myocardial infarction comprising administering the small molecule pyrazolopyrimidine class Src family tyrosine kinase inhibitors taught by Boschelli et al.

Thus, someone of skill in the art at the time the instant invention was made would have found it obvious to create the instant claimed invention with reasonable predictability.

Claim Rejections – 35 USC 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 6-12, 16, and 33-37 are rejected under 35 U.S.C. 112, first paragraph,while the specification is enabling for treating or reducing reperfusion injury in a subject suffering from myocardial infarction, does not reasonably provide enablement preventing reperfusion injury or cure myocardial infarction. To be enabling, the specification of the patent application must teach those skilled in the art how to

make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if its is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth in *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman* 230 USPQ 546 (BdApls 1986) at 547 the court cited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re*

Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art.

The invention in general relates to a method of treating, preventing, or reducing reperfusion injury or post-pump syndrome by administering an inhibitor of vascular endothelial growth factor-mediated vascular permeability.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. It is noted that the chemical, pharmaceutical, and cosmetic arts are generally unpredictable, requiring each embodiment to be individually assessed for chemical, pharmaceutical, and personal effects. The more unpredictable an area, the more specific enablement is necessary in order to satisfy the statue. (see *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970)).

Cheresh et al. (US Patent Application Pub. No. 2003/0130209) a method for treating a patient suffering from a myocardial infarction comprising administering to the patient a therapeutically effective amount of a pharmaceutical composition comprising a chemical Src family tyrosine kinase inhibitor, wherein the chemical inhibitor is selected from the group consisting of a pyrazolopyrimidine class Src family tyrosine kinase inhibitor, a macrocyclic dienone class Src family tyrosine kinase inhibitor, a pyrido[2,3-d]pyrimidine class Src family tyrosine kinase inhibitor, and a mixture thereof (see

reference claims 1-2). Applicant elected "myocardial infarction" as the disease species. Cherish et al. teach compositions comprising said compounds are administered intravenously (para 0060-0061). Instant claim 12 recites the term "intravenously." Cherish et al. teach that an optimal level of inhibition was achieved at a dosage of about 1.5 mg/kg of AGL1872; however, a dosage of about 3 mg/kg did not result in any significant reduction in infarct size (para 0103). Cherish et al. teach Cherish teach that Src appears to regulate tissue damage by influencing VEGF-mediated vasopermeability and thus represents a novel therapeutic target in the pathophysiology of myocardial ischemia (para 0106). Cherish et al. teach that treatment with the Src family tyrosine kinase inhibitor resulted in a decrease in infarct size and area at risk in a dose dependent manner within 24 hours postoperative(para 0104). A maximum inhibition of about 68% ($p<0.05$) in infarct size was achieved at a dosage of about 1.5 mg/kg of the inhibitor delivered about 45 minutes after induction of ischemia (FIG. 13). See para 0104. The inhibitor was also effective when given about 6 hours after induction of ischemia, resulting in a decrease of about 42% in the infarct size ($p<0.05$). See para 0104. Cheresh et al. teach that the methods of the present invention are well suited for the specific amelioration of VP induced tissue damage, particularly that resulting from myocardial infarction, because the targeted inhibition of Src family tyrosine kinase action focuses inhibition on VP without a long term effect on other VEGF-induced responses which can be beneficial to recovery from injury (para 0105). Cherish et al. teach that the use of synthetic, relatively small-molecule chemical inhibitors is in general safer and more manageable that the use of the relatively larger proteins (para 0107).

2. The breadth of the claims

The instant claims are relatively broad in scope. For example, claims 1 and 33 recite the terms "treating, preventing, or reducing reperfusion injury" following myocardial infarction. The term "preventing," given its broadest reasonable possible interpretation is construed to mean cure or absolute absence of any and all reperfusion injury. Claims 1 and 33 also recite the term "administering" which is very broad as drugs can be administered via a multiplicity of different routes that would result in significant variability in the pharmacokinetic and pharmacodynamic effects of the administered drug. Thus, the level of reliability and predictability in practicing the instant claimed method would be greatly diminished depending on the route of administration employed for administering the compounds encompassed by the claims.

3. The amount of direction or guidance provided and the presence or absence of working examples

Applicant do disclose working examples to show that SKI-606 reduces reperfusion injury in a rat model (see specification, pages 9-10, and Fig. 22B). However, there is a significant difference between treating myocardial infarction and completely curing myocardial infarction or perfusion injury following a myocardial infarction. Furthermore, the examples do not support applicant's assertion that the instant claimed method prevents/cures myocardial infarction.

4. The quantity of experimentation necessary

In view of the uncertainty and unpredictability of the art as evidenced by the discussion of the prior art, it is reasonable to surmise that this level of uncertainty in

the art would require one skilled in the art to conduct more than routine experimentation in order to practice the claimed invention commensurate with the scope of the claims.

For the reasons stated above, 1-3, 6-12, 16, and 33-37 are rejected under 35 USC 112, first paragraph, for lack of scope enablement because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims.

Claim rejections – 35 USC 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 USC 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

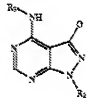
Claims 9, and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9, and 36 recite one or more of the following terms: "PPI," "PP2," and "SKI-606," but fails to state the full meaning of the terms at the first occurrence the terms are recited in the claim. This limitation is vague and indefinite because it is not clear what these terms mean. It is suggested that this specific rejection may be overcome by either replacing each term with the full name or, alternatively, amend the claim by inserting the full name in parenthesis at the first occurrence of each term in the claim set.

Relevant Art of Record

The below cited art made of record and relied upon are considered pertinent to applicant's invention.

Hirst et al. (US Patent 6,660,744) teach methods for treating various conditions, including cardiovascular conditions, comprising administering pyrazolopyrimidine protein kinase inhibitory compounds for promoting angiogenesis, wherein the compounds have a core structure as shown below (see col. 9 line 31 to col. 12, line 35):



the racemic-diastereomeric mixtures, optical isomers, pharmaceutically-acceptable salts, prodrugs or biologically active metabolites thereof wherein:

Hirst et al. teach that these compounds may be administered to a human patient in therapeutically effective amounts to treat or ameliorate vascular permeability edema and associated disorders via various routes, including prevention or attenuation of inappropriate neovascularizaton; the compounds may be administered via various routes, including the intravenous route (col. 47, lines 19-43). Hirst et al. teach that protein kinase inhibitors have various utilities due to the fact that VEGF stimulation is believed to play an important role in various pathological processes including tumor ascites, cerebral and pulmonary edema, ..., ischemia, diabetic complications, ..." See col. 45, line 14 to col. 46,line 50.

Cheresh et al. (US Patent Application Pub. No. 2004/0214836) is considered post-dated art, which is directed to the identical subject matter of the instant application (see abstract and claim 12).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http:pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 800-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

24 April 2008
/C. R./
Examiner, Art Unit 1611